

**RESPONSE**

With this response, claim 1 has been amended. Claims 1, 9, 17, 28, and 29 are currently pending and claims 19-25 and 30-34 have been canceled. Applicants reserve the right to pursue the subject matter of any canceled claims in continuation or divisional applications.

***Claim Objections***

1) The Examiner has objected to claim 1 because claim 1 has Ring A defined as a morpholinyl ring, however, group (iii) which is substituted on the morpholinyl ring states that substituent can be "0-2 oxo groups on a ring sulfur". In an effort to expedite prosecution, Applicants have amended claim 1 to delete "or 0-2 oxo groups on a ring sulfur" at the suggestion of the Examiner. Applicants thus respectfully request that the objection to claim 1 be withdrawn.

***Rejection under 35 U.S.C. 112, second paragraph:***

2) The Examiner has rejected claims 1, 9, and 17 and states that the phrase "amino acid side chain" renders the claims indefinite as it is unclear what substituents are considered "amino acid side chains". The Examiner further states that it is unclear what are "amino acid side chains" as there is no guidance on how to determine if a substituent is an "amino acid side chain". Applicants respectfully disagree and maintain the arguments previously presented; however, in an effort to expedite prosecution, Applicants have deleted reference to "amino acid side chains".

***Rejection under 35 U.S.C. § 103(a):***

The Examiner has maintained the rejection of claims 1, 9, and 17 as being unpatentable over Castro *et al.* Specifically, the Examiner states that the difference between the prior art and the claims at issue is that the prior art provides an unsubstituted ring A, but ring A of the instant claims is substituted by at least one of C(R<sup>9</sup>)<sub>3</sub>, W-G, or G, wherein C(R<sup>9</sup>)<sub>3</sub> can be methyl. The Examiner further states that the substitution of a methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results and that the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (i.e., inhibitors of IKK).

In response to the arguments presented by Applicants in the Office Action Response dated August 21, 2007, the Examiner has asserted that these arguments are not persuasive and asserts that (1) the motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity; (2) the reasonable expectation of success is seen in that it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results; and (3) the prior art teaches and suggests all of the

claim limitations as Castro *et al* disclose the compound 35 and registry number 590398-98-4 useful to inhibit IKK for the treatment of certain inflammatory diseases and the only difference between the prior art and the claims at issue is that the prior art provides an unsubstituted A ring wherein ring A of the instant claims is substituted by at least one of  $-C(R^9)_3$ , W-G, or G, wherein  $-C(R^9)_3$  can be methyl. See Office Action dated 01/09/2008, pp. 3-4.

Applicants respectfully disagree and maintain that that the Examiner has not established a *prima facie* case of obviousness and thus claims 1, 8, 9 and 17 are not obvious over Castro *et al*.

As stated in MPEP § 2142, in order to establish a *prima facie* case of obviousness: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine the teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success *must both be found in the prior art, and not based on applicant's disclosure*. MPEP §2142 also states that impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. Additionally, ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language *and considering the invention and the prior art as a whole*. See MPEP § 2141.02.

Applicants respectfully submit that there is no suggestion or motivation in Castro *et al.*, alone or combined with knowledge generally available in the art, to modify the reference to arrive at the claimed invention, nor does it provide any reasonable expectation that modification of the morpholine ring to include methyl would successfully yield compounds having activity against IKK that would be useful for the diseases and disorders described by the Applicants. Applicants would also like to point out that in addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of “adequate support in the prior art” for the change in structure. See *In re Grabiak*, 769 F.2d 729, 731-32 (*Fed. Cir.* 1985). Furthermore, Applicants respectfully assert that the Examiner must consider the prior art as a whole.

As stated previously, Castro *et al.*, when considered as a whole, teach away from the use of morpholine substituents. For example, in Table 4 (which lists a variety of analogues prepared along with their activity against IKK), compound 35, the compound that is cited by the Examiner, has an  $IC_{50}$  of greater than 20, whereas other compounds that do not have the morpholine substituent (e.g., compound 33) have increased activity (0.7  $\mu$ M for compound 33). Thus, in view of the disclosure of Castro *et al.* as a whole, one of ordinary skill in the art would not be motivated to select the morpholine substituent for modification, nor would they have any reasonable expectation that the use or modification of the morpholine substituent would successfully lead to compounds having increased activity as inhibitors of IKK. Similar to the situation in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d

1350 (Fed. Cir. 2007), considering the subject invention as a whole would have directed one of ordinary skill in the art away from the modification of morpholino compounds, and thus the prior art does not provide the suggestion for making the specific molecular modifications necessary to achieve the claimed invention.

In view of the remarks detailed above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) of claims 1, 9, and 17 be withdrawn by the Examiner.

***Provisional nonstatutory obviousness-type double patenting rejection:***

The Examiner has provisionally rejected claims 1, 9, and 17 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 11/101,998. Applicants respectfully submit that the claims of the present application are in condition for allowance and respectfully request notification of such. Applicants also request withdrawal of the provisional nonstatutory double patenting rejection upon allowance of the pending claims. See MPEP § 804

**REMARKS**

Entry of the amendments and arguments made herein is respectfully requested, and Applicants respectfully submit that pending claims 1, 9, 17, 28, and 29 are in condition for allowance. Applicants would additionally like to thank the Examiner for careful review of the application. If the Examiner believes that a telephone call would expedite prosecution of the above-referenced application, the Examiner is invited to call Karoline Shair at (617) 444-3227.

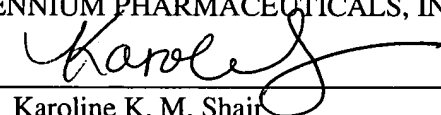
In the event any additional fees are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

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Respectfully submitted,

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By



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